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**From:** Gibbons, Catherine [Gibbons.Catherine@epa.gov]  
**Sent:** 9/4/2013 1:35:17 PM  
**To:** Vulimiri, Suryanarayana [Vulimiri.Sury@epa.gov]; Kraft, Andrew [Kraft.Andrew@epa.gov]; Keshava, Nagalakshmi [Keshava.Nagu@epa.gov]  
**CC:** Sonawane, Bob [Sonawane.Bob@epa.gov]; Guyton, Kate [Guyton.Kate@epa.gov]; Fritz, Jason [Fritz.Jason@epa.gov]; Glenn, Barbara [Glenn.Barbara@epa.gov]  
**Subject:** RE: FA-Genetox Revised  
**Attachments:** FA genetox table revisions 9-3-13\_cfg.docx

Sury,

## Ex. 5 Deliberative Process (DP)

# Ex. 5 Deliberative Process (DP)

Please do share revisions before they are complete for more immediate feedback, and don't hesitate to contact me if you 'd like to discuss any of these suggestions further.

Thank you,

Catherine

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**From:** Vulimiri, Suryanarayana

**Sent:** Thursday, August 29, 2013 2:20 PM

**To:** Kraft, Andrew; Keshava, Nagalakshmi

**Cc:** Sonawane, Bob; Gibbons, Catherine; Guyton, Kate; Fritz, Jason; Glenn, Barbara

**Subject:** RE: FA-Genetox Revised

Andrew,

I got little late into the meeting and was not there at the end of the meeting when you had some further discussion. So if I am missing some points, or something not correct, please feel free to add/revise as necessary.

Here are some main points:

- Catherine will come up with the GeneTox table format and Sury will update the tables with test article information, cytotoxicity and cell proliferation info (if available) – by September 13<sup>th</sup> Friday (2 wks).
- Sury will move the info on oral and i.p. routes to the respective end points from inhalation studies in the Summary synthesis – after the Table update is completed.
- Sury (with Catherine and Nagu):To revise the GeneTox Summary Synthesis keeping them together as a thread – One week after the Tables are revised (~September 20<sup>th</sup>).

- Sury (with Jason): To check if there are any studies on hprt mutations in splenocytes with formaldehyde exposure – September 13<sup>th</sup> (1 wk)
- Sury (with Andrew): To come out with the paragraph on the Systematic review of literature after the last FA draft (which is already there, which needs some revision) – September 20<sup>th</sup>.
- Nagu and Amanda: To work on the study quality evaluation of Epi studies from the GeneTox point of view, reorganize the Table and interpret the data – September 13<sup>th</sup>
- Bob mentioned about Epigenetics info, Jason mentioned it is in the MOA section. I am not sure any decision has been taken on this.

Please feel free if I missed anything.

Sury

**Sury Vulimiri, Ph.D., DABT**

National Center for Environmental Assessment, Office of Research & Development, US EPA

Phone: 919-541-3558 | Fax: 919-541-0245 | [vulimiri.sury@epa.gov](mailto:vulimiri.sury@epa.gov)

USPS Address: US EPA, Research Triangle Park, NC 27711

Physical Address: US EPA, M.D. B243-01, 109 T.W. Alexander Dr, Research Triangle Park, NC 27711

UPS, FEDEX & Other Delivery Address: U.S. EPA, M.D. B243-01, 4930 Old Page Rd, Durham, NC 27703

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**From:** Kraft, Andrew

**Sent:** Thursday, August 29, 2013 1:39 PM

**To:** Keshava, Nagalakshmi; Vulimiri, Suryanarayana

**Cc:** Sonawane, Bob; Gibbons, Catherine; Guyton, Kate; Fritz, Jason; Glenn, Barbara; Kraft, Andrew

**Subject:** RE: FA-Genetox Revised

Hi Sury,

Can you please provide the group with a summary of today's meeting, as you understood it? In particular, can you please indicate what the next steps are, who will be doing them working with whom, and how long we expect this to take (i.e., what are the action items)?

Please note, after the call we had some further discussion. As a result, I would like you to focus first on updating the tables to include the relevant information related to test article, cell proliferation, and cytotoxicity, rather than spending your time on the synthesis at this point. While you are adding clarifying details to the tables, can you please also incorporate the forthcoming suggestions from Catherine (there is no need to wait for her suggestions before you get started) regarding table organization?

Thanks,  
Andrew

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**From:** Fritz, Jason

**Sent:** Thursday, August 29, 2013 9:57 AM

**To:** Kraft, Andrew; Keshava, Nagalakshmi; Vulimiri, Suryanarayana; Glenn, Barbara

**Cc:** Sonawane, Bob; Gibbons, Catherine; Chiu, Weihsueh; Subramaniam, Ravi; Guyton, Kate

**Subject:** RE: FA-Genetox Revised

Hello,

As we discussed back in July, for the URT MOA section we are still planning on a section where the main pertinent observations from the GeneTox database are presented in a small "mechanistic evidence" subsection, supporting the

contribution of mutagenicity to FA-induced URT/POE cancer, before we launch into the Bradford-Hill-type considerations discussions.

Suri sent me a summary which can be used as a placeholder while we revise the URT MOA from Lynn's latest draft, and we can replace that placeholder genetox section with whatever more finalized version once that becomes ready. Revisions to Lynn's URT MOA draft are ongoing... we'll send out a revision to the ToxPath workgroup when we have something we like more ☺

jf

Jason M. Fritz, Ph.D.  
Toxicologist  
U.S. EPA  
ORD/NCEA/IRIS  
1200 Pennsylvania Ave., N.W.  
Washington, D.C., 20460  
703-347-0332

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**From:** Kraft, Andrew  
**Sent:** Thursday, August 29, 2013 9:26 AM  
**To:** Keshava, Nagalakshmi; Vulimiri, Suryanarayana; Glenn, Barbara  
**Cc:** Sonawane, Bob; Gibbons, Catherine; Fritz, Jason; Chiu, Weihsueh; Subramaniam, Ravi  
**Subject:** RE: FA-Genetox Revised

Thanks, Nagu. We can discuss organization at 10:30. I only looked at the summary, to be honest- I didn't realize the order of the full text was going to be revised!

Ex. 5 Deliberative Process (DP)

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Jason would have the most current MOA draft, so I will ask him to send you that-please note that it is under revision.

I am going to forward the invite to Ravi. He has an interest, and may want to attend.

-Andrew

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**From:** Keshava, Nagalakshmi  
**Sent:** Thursday, August 29, 2013 9:10 AM  
**To:** Kraft, Andrew; Vulimiri, Suryanarayana; Glenn, Barbara  
**Cc:** Sonawane, Bob; Gibbons, Catherine; Fritz, Jason; Chiu, Weihsueh  
**Subject:** RE: FA-Genetox Revised

Hi Andrew:

## Ex. 5 Deliberative Process (DP)

# Ex. 5 Deliberative Process (DP)

The summary can be organized in any way that would best fit the rest of the document. Lets discuss at the meeting.

Also, could you please share the MOA section of the document, just to see how the genotoxicity data is interpreted in the main document – no rush, whenever it is ready.

Thanks  
Nagu

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**From:** Kraft, Andrew  
**Sent:** Tuesday, August 27, 2013 10:13 AM  
**To:** Vulimiri, Suryanarayana; Glenn, Barbara  
**Cc:** Sonawane, Bob; Gibbons, Catherine; Keshava, Nagalakshmi; Fritz, Jason  
**Subject:** RE: FA-Genetox Revised

Thanks, Sury.

# Ex. 5 Deliberative Process (DP)

This would be how I think the Tox Pathways recommendation was meant to be interpreted, but I have cc'd Catherine, Nagu and Jason to get their feedback. I think this is a critical issue, so I am happy to schedule a meeting to discuss, if you feel that is necessary.

-Andrew

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**From:** Vulimiri, Suryanarayana  
**Sent:** Tuesday, August 27, 2013 10:02 AM  
**To:** Kraft, Andrew; Glenn, Barbara  
**Cc:** Sonawane, Bob  
**Subject:** RE: FA-Genetox Revised

Hi Andrew,

Good morning. Thanks for the mail. Regarding the questions you asked...

# Ex. 5 Deliberative Process (DP)

**Regarding the status of the ADME:** I am working on addressing these comments. We had good discussion but sometimes it is going outside the scope. I will finish it by next week. Regarding the question of rushing or not, I would like to know the time frame for responding, so that I can plan better.

**Regarding the status of GeneTox:** The GeneTox revision took a long time with the number of comments to respond. Apparently, NAS did not have any major issues for GeneTox; in fact they appreciated the organization and presentation. I gave my response and synthesis of the GeneTox summary to the WG. I can get back to that only after finishing the ADME section. After I get the study quality review and revision of Table with human GeneTox studies, I will address those issues. So from that point of view the GeneTox section has some more work to do.

**General feeling:**

# Ex. 5 Deliberative Process (DP)

OK, I will get back to my ADME revision now. Also, I am working on my review of the NPC MOA (from Lynn Adams) and will send my comments to Jason.

Sury

**Sury Vulimiri, Ph.D., DABT**

National Center for Environmental Assessment, Office of Research & Development, US EPA

Phone: 919-541-3558 | Fax: 919-541-0245 | [vulimiri.sury@epa.gov](mailto:vulimiri.sury@epa.gov)

USPS Address: US EPA, Research Triangle Park, NC 27711

Physical Address: US EPA, M.D. B243-01, 109 T.W. Alexander Dr, Research Triangle Park, NC 27711

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**From:** Kraft, Andrew

**Sent:** Tuesday, August 27, 2013 8:13 AM

**To:** Vulimiri, Suryanarayana; Glenn, Barbara

**Cc:** Sonawane, Bob; Kraft, Andrew

**Subject:** RE: FA-Genetox Revised

Thank you for revising this so quickly, Sury. I like the summary layout. I had just a few, quick thoughts from a rapid skim of the attachments:

## Ex. 5 Deliberative Process (DP)

Please note, I didn't anticipate you being done with the ADME and genetox sections (from a scheduling perspective, and not including the endogenous formaldehyde issue) until the week of September 8<sup>th</sup>, so please do not rush... take the time you need.

Thank you again for turning this around so quickly,  
Andrew

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**From:** Vulimiri, Suryanarayana  
**Sent:** Monday, August 26, 2013 5:17 PM  
**To:** Kraft, Andrew; Glenn, Barbara  
**Cc:** Sonawane, Bob  
**Subject:** FW: FA-Genetox Revised

Hi Andrew/Barbara,

Sorry, I forgot to cc you. Regarding the FA-GeneTox section here is the revised draft with track changes in response to the comments provided by the ToxPath/GeneTox WG. Also, see a separate file where I provided synthesis for the GeneTox Summary. I will work with Nagu and Amanda once I get the review of the Study Quality criteria from Amanda.

We had a series of discussions with the PKWG group after receiving their comments. Also, at the request of selected members of the PKWG we had discussion specifically on endogenous formaldehyde and methanediol issues. After sending the GeneTox revised section, I got back on to the ADME part and started revising the document. I will be able to send the revised draft by early next week.

Sury

**Sury Vulimiri, Ph.D., DABT**

National Center for Environmental Assessment, Office of Research & Development, US EPA

Phone: 919-541-3558 | Fax: 919-541-0245 | [vulimiri.sury@epa.gov](mailto:vulimiri.sury@epa.gov)

USPS Address: US EPA, Research Triangle Park, NC 27711

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**From:** Vulimiri, Suryanarayana  
**Sent:** Monday, August 26, 2013 12:07 PM  
**To:** Keshava, Nagalakshmi; Gibbons, Catherine  
**Cc:** Sonawane, Bob; Vulimiri, Suryanarayana  
**Subject:** FA-Genetox Revised

Hi Nagu and Catherine,

Good morning. Thank you very much for providing the comments on the FA-GeneTox section. Since there were several comments it took a while in revising the draft. Also, being a huge file I faced issues while saving the draft and sometimes

lost some text which also added to the delay. It would be easier to work with one section separately. Anyway, here is the revised version with track changes.

I have addressed most of the comments provided by the reviewers. As we discussed and agreed before, reorganizing the Tables is a huge task, so I have not done that at the moment. Also, one issue about study quality of human studies is not touched now. I guess Amanda is working on that and understand that she will be reorganizing the Table for human studies.

As recommended by the reviewers, I have synthesized the summary with greater detail citing the weight of evidence. For convenience of the reviewers, I prepared a separate file for the synthesis of WOE for GeneTox, which up on review can be added to the GeneTox section at the end.

Sury

**Sury Vulimiri, Ph.D., DABT**

National Center for Environmental Assessment, Office of Research & Development, US EPA

Phone: 919-541-3558 | Fax: 919-541-0245 | [vulimiri.sury@epa.gov](mailto:vulimiri.sury@epa.gov)

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